

Adenosine Myocardial Protection

Preliminary Results of a Phase II Clinical Trial

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Objective

To evaluate the safety, tolerance, and efficacy of adenosine in patients undergoing coronary artery bypass surgery.

Summary Background Data

Inadequate myocardial protection in patients undergoing coronary artery bypass surgery contributes to overall hospital morbidity and mortality. For this reason, new pharmacologic agents are under investigation to protect the regionally and globally ischemic heart.

Methods

In a double-blind, placebo-controlled trial, 253 patients were randomized to one of three cohorts. The treatment arms consisted of the intraoperative administration of cold blood cardioplegia, blood cardioplegia containing 500 μ M adenosine, and blood cardioplegia containing 2 mM adenosine. Patients receiving adenosine cardioplegia were also given an infusion of adenosine (200 μ g/kg/min) 10 minutes before and 15 min-

utes after removal of the aortic crossclamp. Invasive and non-invasive measurements of ventricular performance were obtained before, during, and after surgery.

Results

The high-dose adenosine cohort was associated with a trend toward a decrease in high-dose dopamine support and a lower incidence of myocardial infarction. A composite outcome analysis demonstrated that patients who received high-dose adenosine were less likely to experience one of five adverse events: high-dose dopamine use, epinephrine use, insertion of intraaortic balloon pump, myocardial infarction, or death. The operative mortality rate for all patients studied was 3.6% (9/253).

Conclusions

Adenosine treatment is safe and well tolerated and may be associated with fewer postoperative complications.

With the advent of coronary artery bypass surgery in 1967, the need to develop new methodologies to protect the arrested heart became apparent. This resulted in a marked proliferation of pharmacologic approaches designed to enhance the heart's tolerance to ischemia and maximize qui-

escent operative time. Although we now have a much better understanding of the cellular and subcellular mechanisms that contribute to postischemic myocardial dysfunction, the problem of inadequate myocardial protection persists. This is reflected in the marked use of inotropic agents in the postoperative period independent of the magnitude of the surgical procedure (e.g., coronary artery bypass surgery, combined bypass and valve surgery, or cardiac transplantation). Whether the injury is reversible (myocardial stunning) or irreversible (myocardial infarction [MI]), new methods and strategies to enhance cardioprotection need to be identified.

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One agent that is receiving increased attention is the nucleoside adenosine. Considerable experimental evidence exists that adenosine is a cardioprotective agent independent of its well-known vascular smooth muscle relaxing effect and its antiadrenergic and negative chronotropic and dromotropic properties.¹ This phenomenon appears to be mediated primarily by activation of the A₁ receptor coupled to guanine nucleotide inhibitory binding (G_i) proteins.^{1,2} Although intensive efforts are underway to elucidate the intracellular end effector(s) of adenosine's beneficial effects, it has not been conclusively demonstrated that adenosine is cardioprotective in humans. This is partly due to the lack of prospective, randomized, blinded studies specifically designed to evaluate the safety and efficacy of adenosine in the clinical setting of heart surgery.

In 1997, Mentzer et al³ reported the results of a single-center, open-label pilot study in which adenosine was added to conventional hyperkalemic cold blood cardioplegia in patients undergoing elective cardiac surgery. The purpose of that study was to evaluate the safety and tolerance of the additive in the context of increasing concentrations ranging from 100 μ M to 2 mM. A sixth arm of the study included patients who were pretreated with intravenous infusions of adenosine. The results of the trial indicated that adenosine was safe and well tolerated even at high concentrations. Patients who received high-dose adenosine also appeared to require less dopamine support during the first 24 hours after surgery.

On the basis of these findings, as well as other preclinical studies, a phase II clinical trial was initiated to determine whether adenosine is a safe and effective cardioprotective agent when used during coronary artery bypass surgery in patients with depressed ventricular function.

METHODS

Patient Selection

The study was approved by the local institutional review board at each participating site. Study patients included those who were electively scheduled for coronary artery bypass surgery and had an ejection fraction of ≤ 0.40 . Exclusion criteria included known or suspected pregnancy, known hypersensitivity to adenosine, and enrollment in another clinical trial study.

Study Design

Informed consent was obtained from each patient enrolled in the study. This was a double-blind, placebo-controlled, parallel-treatment, multicenter clinical trial. A total of 253 patients were enrolled. They were divided into three cohorts:

- Group A patients (placebo, $n = 84$) were given standard hyperkalemic cold blood cardioplegia.
- Group B patients (low-dose adenosine, $n = 84$) were

given hyperkalemic cold blood cardioplegia containing 500 μ M adenosine.

- Group C patients (high-dose adenosine, $n = 85$) were given hyperkalemic cold blood cardioplegia containing 2 mM adenosine.

The patients who received adenosine cardioplegia were also exposed to a 10-minute adenosine pretreatment infusion (200 μ g/kg/min) immediately before application of the aortic crossclamp and a 15-minute adenosine reperfusion infusion (200 μ g/kg/min) immediately after removing the crossclamp.

Before surgery, patients were evaluated for the degree of ischemic disease by history, echocardiography, and cardiac catheterization. In the operating room, hemodynamic measurements were obtained and recorded just before initiating cardiopulmonary bypass and at 15, 30, 45, and 60 minutes and 2, 3, 4, 6, and 8 hours after cessation of bypass. In patients requiring intravenous inotropic medications in the postoperative period, hemodynamic monitoring was continued with measurements of specified parameters every 2 hours for 24 hours and then every 4 hours until the inotropic medications were discontinued or it was ascertained that monitoring was no longer helpful in the management of the patient.

Invasive hemodynamic measurements included systolic blood pressure, heart rate, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output (CO). The cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance, right ventricular stroke work index, and left ventricular stroke index were derived. The CO measurements were obtained using a thermodilution catheter and computer. Noninvasive heart function studies included 12-lead electrocardiograms, preoperative stress dobutamine echocardiography, and pre- and postoperative transthoracic and transesophageal echocardiograms. Patients were monitored from the time of enrollment to follow-up 4 to 6 weeks after discharge from the hospital. This included routine blood work and chemistries, arterial blood gases, pH, creatine kinase (CK)-MB concentrations, and pulse oximetry.

Outcomes

The prespecified primary end points in this study were:

- Reduction in total dopamine use during the first 7 days
- Reduction in all inotropic support required during the first 7 days
- Reduction in the use of dopamine >5 μ g/kg/min.

There were 21 secondary end points, including improvement in postoperative hemodynamics, reduction in the use of the intraaortic balloon pump, reduction in the incidence of MI, and decrease in the mortality rate. Diagnosis of MI required the confirmation of two of the following criteria:

- 12-lead electrocardiogram with new and persistent Q waves
- CK-MB >30 IU/L or >5.9 ng/ml
- CK index >2.7
- Echocardiography demonstrating new wall motion abnormalities.

An independent data and safety monitoring panel reviewed the data at predetermined time intervals and provided interim patient safety reports.

Data Analysis

All patients who received study treatment (placebo, low- or high-dose adenosine) and underwent coronary bypass surgery were included in the intent-to-treat analysis. Categorical primary and secondary end points were analyzed using the Pearson chi square test, comparing the percentage of patients in the placebo group to the low- and high-dose adenosine groups. The continuous hemodynamic profiles were analyzed using a repeated measures analysis to assess rate of change from baseline values.⁴ To take into account the baseline values for each patient, the percentage change from baseline was computed for each hemodynamic outcome. The hemodynamic outcomes were heart rate, systolic blood pressure, cardiac index, pulmonary capillary wedge pressure, central venous pressure, pulmonary artery pressure, left ventricular stroke index, and right ventricular stroke work index. A repeated measures analysis was used to analyze the percentage change from baseline of these outcomes over the first 24 hours off cardiopulmonary bypass for each treatment. In the statistical model, the interaction of time and treatment tested whether the slopes of the lines that pass through the time points of each treatment were significantly different from one another at a level of 5%. When the time by treatment interaction was significant, a statistical comparison of each pair of treatment slopes was performed using the least significant difference pairwise procedure. The slopes were interpreted as an increase or decrease in the percentage change of the hemodynamic outcomes from baseline over time. A compound symmetry structure was used to model the covariances and variances of the time points. All statistical testing was performed with SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Demographics

Two hundred fifty-three patients were enrolled and completed the study. The medical history (*e.g.*, incidence of congestive heart failure, angina, arrhythmias, prior MI, previous coronary artery angioplasty, and previous coronary artery bypass surgery) was similar among the three treatment groups. Likewise, there were no differences with respect to mean age, gender, ejection fraction, crossclamp time, cardiopulmonary bypass time, perioperative hemoglo-

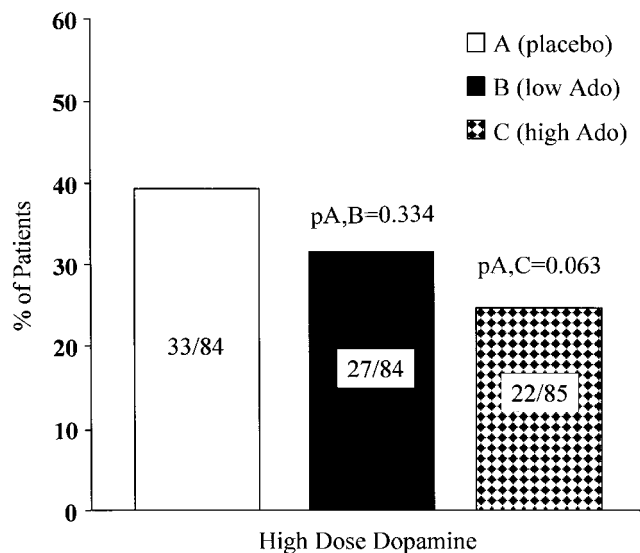


Figure 1. Effects of low- and high-dose adenosine treatments on the number of patients requiring high-dose dopamine (>5 µg/kg/min). The low-dose adenosine group received 500 µM adenosine in the blood cardioplegia, the high-dose group 2 mM adenosine. Both groups were treated with a 200-µg/kg/min infusion immediately before and after removal of the aortic crossclamp.

bin levels, and platelet counts. The total duration of cardioplegia and the total volume of cardioplegia administered to the patients were also similar.

Use of Inotropic Support

In the first 7 days after surgery, 77% (65/84) of the patients in the placebo group, 71% (60/84) of the patients in the low-dose adenosine group, and 79% (67/85) of the patients in the high-dose adenosine group received dopamine. There was no significant difference between the placebo and either the low- or high-dose adenosine cohorts. Likewise, the use of any inotropic agent (dopamine, milrinone, amrinone, epinephrine, norepinephrine, dobutamine, or isoproterenol) during the first 7 days after surgery was similar (79%, 73%, and 80%). There was a trend toward a reduction in the number of patients requiring high-dose dopamine (>5 µg/kg/min; Fig. 1) and intravenous epinephrine (Fig. 2). Specifically, 39% of the patients in the placebo group received high-dose dopamine *versus* 26% in the high-dose adenosine group. Twenty-five percent of the patients in the placebo group received epinephrine *versus* 14% in the high-dose adenosine group.

Hemodynamic Recovery

There was no significant time by treatment interaction for the hemodynamic variables of central venous pressure, pulmonary artery pressure, left ventricular stroke index, or right ventricular stroke work index. The results for the other hemodynamic parameters are shown in Table 1. The per-

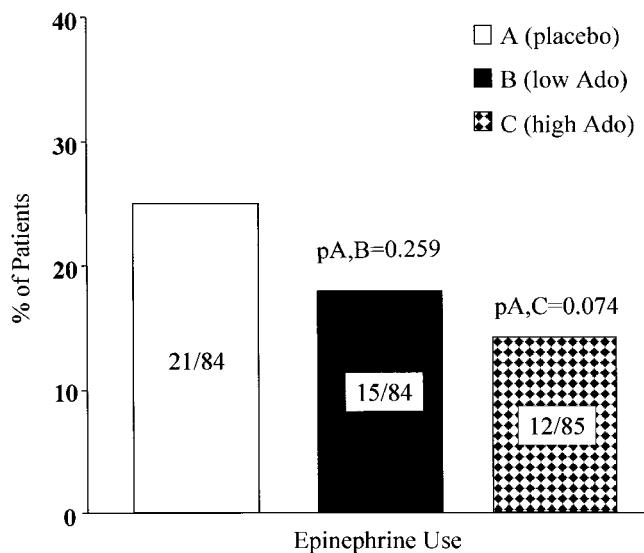


Figure 2. Percentage of patients requiring epinephrine use in the three cohorts.

centage change in systolic blood pressure from baseline was not affected by treatment. With respect to heart rate, there was a significant time by treatment interaction ($p = 0.004$). Pairwise comparison showed that patients in the placebo group were significantly different from the low- and high-dose adenosine groups. Although the absolute mean heart rate was similar among all three groups at baseline (69.6 ± 1.7 , 66.5 ± 1.6 , and 67.4 ± 1.7 beats per minute) and 24 hours after surgery (95.1 ± 3.4 , 90.7 ± 3.6 , and 96.8 ± 5.4 beats per minute), stabilization of the heart rate was achieved sooner in patients receiving high-dose adenosine.

As reflected by the slopes in Table 1, the cardiac index

improved more rapidly in patients receiving high-dose adenosine *versus* placebo treatment ($p = 0.002$). Normalization of pulmonary capillary wedge pressure also occurred more rapidly in the patients receiving high-dose adenosine.

Intraaortic Balloon Pump Insertion, Myocardial Infarction, and Death Rate

Overall, 6.3% (16/253) of the study patients required insertion of the intraaortic balloon pump for low CO. There were nine insertions in the placebo group, two in the low-dose adenosine group, and five in the high-dose adenosine group. The overall incidence of postoperative MI was relatively low (5.1%). Nevertheless, the MI rate in the high-dose adenosine group was lower when compared with the placebo group (1.2% *vs.* 9.5%; Fig. 3).

The overall death rate for the entire study population was 3.6%. There was a trend toward a lower rate in the adenosine-treated patients *versus* the placebo group (1.2%, 3.6%, and 6.0%; Fig. 4). When a composite outcome of high-dose dopamine, epinephrine use, insertion of the intraaortic balloon pump, MI, and death was analyzed (Fig. 5), the percentage of patients experiencing one of these adverse events was lower in patients treated with high-dose adenosine ($p = 0.006$).

DISCUSSION

The major findings of this trial are as follows:

1. The administration of high-dose adenosine in patients undergoing coronary artery bypass surgery using cardiopulmonary bypass is safe and well tolerated.

Table 1. EFFECT OF ADENOSINE TREATMENT ON PERCENTAGE CHANGE IN SELECTED HEMODYNAMIC VARIABLES COMPARED WITH BASELINE DURING FIRST 24 POSTOPERATIVE HOURS

	Cohort	Slope \pm SE	Comparison	p Value
Heart rate	A	0.254 ± 0.079	A <i>vs.</i> B	0.0216
	B	0.510 ± 0.078	B <i>vs.</i> C	Not significant
	C	0.620 ± 0.081	A <i>vs.</i> C	0.0013
Systolic blood pressure	A	0.532 ± 0.061	A <i>vs.</i> B	Not appropriate
	B	0.387 ± 0.060	B <i>vs.</i> C	Not appropriate
	C	0.440 ± 0.063	A <i>vs.</i> C	Not appropriate
Cardiac index	A	0.983 ± 0.109	A <i>vs.</i> B	Not significant
	B	1.130 ± 0.105	B <i>vs.</i> C	0.0277
	C	1.468 ± 0.112	A <i>vs.</i> C	0.0020
Pulmonary capillary wedge pressure	A	0.523 ± 0.272	A <i>vs.</i> B	Not significant
	B	0.688 ± 0.249	B <i>vs.</i> C	0.0001
	C	-0.869 ± 0.288	A <i>vs.</i> C	0.0005

Data are presented as the mean slope of the line \pm SE for each outcome in each treatment. The slopes are interpreted as the increase or decrease of the percentage of the hemodynamic outcome from baseline for every hour of time during the first 24 hours off bypass.

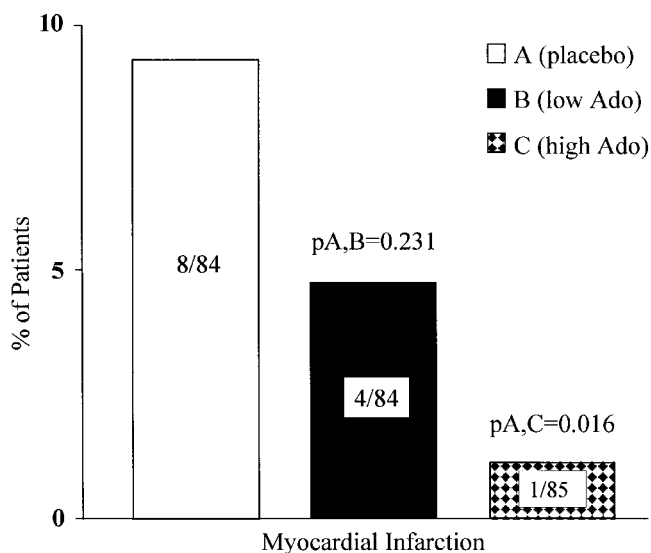


Figure 3. The effects of placebo and low- and high-dose adenosine treatments on the incidence of perioperative myocardial infarction. The overall incidence of myocardial infarction was 5.1%.

2. The use of adenosine may be associated with improved postoperative hemodynamic function.
3. Adenosine treatment, in the context of this study, may be associated with a decrease in morbidity and mortality rates.

These results support the hypothesis that adenosine is a cardioprotective agent in humans.

Although the etiology of postoperative myocardial dysfunction may be multifactorial, low CO requiring inotropic support after open heart surgery is related, in part, to stunning or irreversible injury (MI).^{5,6} This explains why as

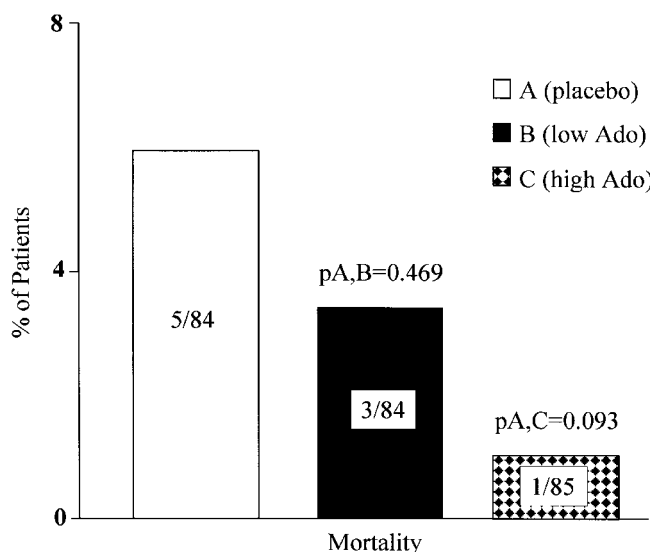


Figure 4. Effects of low- and high-dose adenosine treatments on the mortality rate. The overall mortality rate was 3.5%.

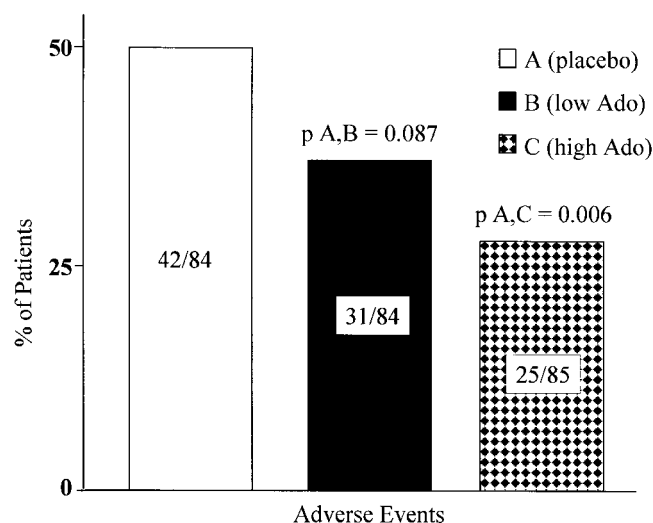


Figure 5. Effects of the two adenosine treatments on adverse events (high-dose dopamine, epinephrine use, insertion of intraaortic balloon pump, myocardial infarction, or death).

many as 20% to 25% of the patients who undergo open heart surgery may require some degree of inotropic support to sustain separation from cardiopulmonary bypass. Although intuitively one would expect that there may be a greater need for inotropic support in patients with reduced left ventricular function, this study suggests that as many as 75% of the patients who undergo myocardial revascularization with an ejection fraction ≤ 0.40 require substantial inotropic support after surgery.

The rationale for studying adenosine in the setting of open heart surgery is based on the considerable experimental evidence that adenosine reduces both myocardial stunning and infarct size.^{1,2,7-14} Although the exact mechanism underlying the cardioprotective effect of adenosine is unknown, the beneficial effects of this agent appear to be related to activation of specific adenosine receptor subtypes, at least three of which (A_1 , A_{2a} , and A_3) may be involved.^{1,2,10,11} Experimental findings indicate that adenosine is most effective in protecting the reversibly injured heart when administered before ischemia, most likely by activation of cardiac myocyte A_1 and A_3 receptors.^{1,2,10,13} Adenosine has also been shown to improve postischemic myocardial energetics in stunned myocardium,¹² in contrast to the effects of traditional inotropic support.¹³ Preischemic adenosine treatment also reduces experimental myocardial infarct size,^{1,9,10} but there is additional evidence that reperfusion adenosine treatment may also reduce infarct size by its ability to reduce platelet and neutrophil adherence to coronary endothelium.¹¹ Finally, because adenosine is also a potent coronary vasodilator, increased coronary artery blood flow during reperfusion may be beneficial, not only increasing oxygen and the substrate delivery but also enhancing washout of toxic products of ischemia.

Additional experimental observations and the results of recent clinical trials provided the basis for the two adeno-

sine groups in the present clinical trial. Observations in intact animal models have consistently shown that an increase in preischemic interstitial fluid adenosine concentrations is associated with cardioprotection.^{8,9,12} The interstitial fluid bathes the cardiac myocytes, and thus elevated adenosine levels in interstitial fluid are consistent with activation of cardiac myocyte A₁ and A₃ receptors. This provided the rationale for the adenosine pretreatment infusion before adenosine-supplemented cardioplegia. The dose of adenosine in the pretreatment and reperfusion infusions (200 μ g/kg/min) was slightly higher than that used in the phase I study (140 μ g/kg/min), but the low- and high-dose adenosine groups were based on the plasma adenosine concentrations achieved in the single-center trial.³ The additional adenosine reperfusion infusion arm in this trial was included to maximize the agent's inhibitory effects on neutrophils^{11,15} and platelet aggregation,¹⁶ which may contribute to reperfusion injury.

Adenosine has been used clinically for many purposes, the most well known being rapid termination of supraventricular arrhythmias¹⁷ and coronary perfusion imaging.¹⁸ Adenosine has also been used for the management of postoperative systemic and pulmonary hypertension.^{19,20} There have also been several reports of the clinical use of adenosine as a cardioprotective agent. Leeser et al²¹ reported that a 10-minute intracoronary adenosine preconditioning treatment significantly reduced ST segment changes during percutaneous transluminal coronary angioplasty. There are also reports that intravenous adenosine administered to patients with an acute MI is well tolerated and may lead to increased salvage of ischemic tissue.^{22,23} Two phase II clinical trials are underway to evaluate the efficacy of combining adenosine treatment with thrombolytic therapy and/or percutaneous transluminal coronary angioplasty for acute MI.

In addition to the previously mentioned phase I study,³ there are also several other reports of the use of adenosine as a cardioprotective agent during cardiac surgery. Lee et al²⁴ reported that seven patients undergoing coronary revascularization treated with an adenosine infusion before initiation of cardiopulmonary bypass exhibited improved postoperative ventricular performance and reduced CK release compared with patients receiving saline. Fremes et al²⁵ conducted an open-label, nonrandomized phase I study with adenosine supplementation of warm blood cardioplegia. They concluded that adenosine at doses <25 μ M could be safely administered as a supplement to cardioplegic solutions.

More recently, Cohen et al²⁶ reported the results of a phase II double-blind, placebo-controlled clinical trial with adenosine-supplemented cardioplegia. Patients undergoing coronary artery bypass grafting were treated with placebo (saline), warm blood cardioplegia supplemented with 15 μ M adenosine, or cardioplegia supplemented with 50 or 100 μ M adenosine. The primary end points were 30-day mortality, incidence of MI determined by CK-MB values, and low CO. The authors reported no statistically or clinically

relevant differences in outcomes with adenosine cardioplegia. However, there are some potentially important differences between the protocols used in that study and those in the present study. Cohen et al used warm blood cardioplegia (37°C), which they acknowledged limited their use of higher doses of adenosine because of systemic hypotension. Warm blood cardioplegia also results in the more rapid metabolism of adenosine. In the phase I trial with adenosine in cold blood cardioplegia, the use of 100 μ M adenosine was associated with only a minimal increase in plasma adenosine levels.³ Another important difference between this study and others is that our adenosine-treated patients received a pretreatment and reperfusion adenosine infusion. This was based on preclinical findings that cardioprotection is associated with an increase in interstitial fluid adenosine concentrations before ischemia. Finally, approximately 80% of the patients in the study by Cohen et al had preoperative ejection fractions of 0.35 to 0.50, whereas the patients in the present phase II trial had preoperative ejection fractions ≤ 0.40 . As acknowledged by Cohen et al, adenosine may be most effective in patients with compromised left ventricular function.

A major limitation of our trial was the failure to demonstrate a reduction in dopamine use or overall inotropic use, two of the proposed primary end points. Although there was evidence of a trend toward reduction in the use of high-dose dopamine (>5 μ g/kg/min), statistical significance was not achieved at the level of 5%. This may be due, in part, to the high noise-to-signal ratio observed during the study. The criteria and algorithm for administering inotropic agents included indications other than low CO. Patients with a cardiac index of 2.0 to 2.6 L/min/m² could receive inotropic support if the urinary output was <30 ml/hour, systolic blood pressure <100 mm Hg, or pulmonary capillary wedge pressure >20 mm Hg. The latter criteria may explain the relatively high use rate of inotropic agents observed in this study. It underscores the need for a clinical study to differentiate between inotropic use and inotropic dependence, a concept not addressed in this study. When we analyzed the use of dopamine >5 μ g/kg/min, however, only 33% (82/253) of the study patients received high-dose dopamine. Although high-dose dopamine may be only a surrogate marker of inotropic dependence and the degree of myocardial stunning, this frequency of use is not surprising given that the median ejection fraction of patients before surgery was <0.35 . Finally, another limiting factor in this study was the low incidence of MI and death.

Despite these limitations, the hemodynamic data and composite outcome analysis suggest that adenosine has a salutary clinical effect in patients undergoing coronary artery bypass surgery. To demonstrate conclusively, however, that adenosine is cardioprotective, a multicenter clinical trial needs to be performed in which the primary end points are MI and death.

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Discussion

DR. WILLIAM A. BAUMGARTNER (Baltimore, Maryland): Dr. Mentzer and his colleagues have studied the use of adenosine as an adjunct to their cardioplegia solution. Although the authors failed to demonstrate a reduction in dopamine utilization or overall inotropic use, which were two of their primary end points, they did show preliminary data that there was a reduction in operative mortality and myocardial infarction associated with the use of high-dose adenosine.

The authors have chosen an important issue to investigate. In virtually all studies looking at operative mortality associated with coronary bypass surgery, left ventricular function is the most important independent risk predictor of outcome. As the authors have demonstrated, the placebo group had an operative mortality of 6% compared to the high-dose adenosine group whose operative mortality was 1.2%. Although these percentages were obtained in low numbers, these preliminary results suggest that high-dose adenosine may be effective.

In our own series of patients, we found similar results in what we would consider a placebo group since we do not use adenosine. Our overall operative mortality for all patients undergoing coronary bypass surgery in 1997 was 2.9%. However, in the 136 patients whose left ventricular function was less than 40%, our overall operative mortality was 7%, very similar to your findings of 6%.

Bob, I just have a few questions. How much standardization of the operative procedure occurred among the institutions? Were

there any significant differences in the primary and secondary end points among individual institutions?

Based upon your experience so far with this drug, would you recommend the high-dose protocol? And, finally, what are your future plans to study this cardioplegia additive?

Although preliminary, these results have potentially important clinical implications for the care and outcome of patients undergoing coronary bypass surgery.

DR. JOHN W. HAMMON, JR. (Winston-Salem, North Carolina): The study showed some significant changes, and this is a real accomplishment because Dr. Mentzer was laboring under the conflicting influences of his own scientific advisory committee, the regulatory influences of the FDA, and the proprietary interests of the drug company that he worked with. And, therefore, I think he should be congratulated for just literally pulling this off. We were one of the hospitals in which this drug was studied, and I can tell you that the protocol and the conduct of the study was such that it could easily be carried out and standardized, and we felt very lucky to be involved in the investigation.

Dr. Mentzer's study, his preliminary results, does show a distinct trend toward a better outcome in patients receiving adenosine as a cardioplegia additive. The group of adverse outcomes that was mentioned on his last series of slides, including myocardial infarction, high-dose inotrope use, and deaths, would point out a significant influence of adenosine in reducing postischemic stunning in patients that have coronary bypass surgery. This is particularly important in this group of patients, patients who have decreased left ventricular function.

I would like to ask Dr. Mentzer a couple of questions, one practical and one theoretical. My first question centers around the general notion that we have in our profession that our own cardioplegia solution that we use, whatever it is, is the best that can possibly be. We tell our patients that and what have you. And in order to show a difference between our solutions and this new additive, one would have to compare it against some of the additives such as the amino acids, and perhaps lidocaine, that are used in other cardioplegia solutions used around the world today.

The second question is a theoretical question. And that is, because the results of this are preliminary, how are you going to factor out some of the measurements that might indicate less postoperative stunning in your patients? The trends are there to show that there might have been less stunning, but we certainly don't have any proof of that at this point.

And how do you plan to use your data once you have it to influence us in the future? Is this going to be a drug that's going to be useful in routine coronary bypass surgery, or might it be useful in the ultimate of myocardial protection, protection of the donor heart during transplantation?

DR. WALTER H. MERRILL (Nashville, Tennessee): The authors have presented evidence that adenosine, when administered according to the protocol suggested in this study, is safe and well tolerated, it may lead to improvement in postoperative cardiac performance, and it may lead to lower morbidity and mortality rates. The fact that adenosine did not lead to more striking improvement in outcomes may be related to several factors.

First, this study includes only patients undergoing elective coronary bypass grafting, and the patients studied had on average relatively good myocardial function preoperatively. Thus, as a whole, the study patients constitute a relatively low-risk group in which it is difficult to

improve outcomes. Secondly, modern myocardial protection regimens with or without the addition of adenosine have proven to be safe and efficacious, especially in relatively low-risk patients.

I have several questions to ask. First, what is the optimum adenosine regimen? In this study, the high-dose group consistently had better outcomes than the low-dose group. Would even higher doses of adenosine prove to be more effective?

Second, would you speculate as to whether or not adenosine will have even more important cardioprotective benefits in patients with severely compromised function and who are consequently at increased risk to develop perioperative myocardial infarction and death?

And, finally, did you note a reduction in postbypass transfusion requirements similar to those observed in your prior study?

DR. ROBERT M. MENTZER, JR. (Closing Discussion): In response to Dr. Baumgartner's request for standardization, whether or not patients were treated the same way at all the institutions, we did have close monitoring and frequent communication in that regard to insure as best as possible that standardization did occur. We have not done institution-specific analyses, however, to look at variations among the study sites.

In terms of recommending its use—and it's not dissimilar from the question proposed by Dr. Hammon—we're reluctant to recommend utilization of the agent for myocardial protection until we have really conclusively demonstrated that this agent is cardioprotective in humans.

We do have substantial experimental and preclinical data that the concept of ischemic preconditioning, that is, subjecting the heart to a brief period of ischemia followed by a washout, then sustained ischemia, that this ischemic preconditioning can substantially reduce infarct size.

In fact, there are Phase I clinical trials that have just been completed that would suggest that adenosine therapy at the time of thrombolytic therapy and PTCA reduces infarct size in humans. But I would be reluctant, and I think our co-investigators would be reluctant, to suggest the utilization of this agent at this time until we conclusively demonstrate it.

To follow up with Dr. Hammon's comments, we do use adenosine as an agent to protect the ischemic heart. Every time we use the University of Wisconsin preservation solution for heart procurement, we have in that solution 5 mmol adenosine.

With respect to the question regarding the dose and the timing of administration, the dosing actually was determined on the basis of a Phase I clinical trial that we completed approximately 2½ years ago. We had incrementally changing doses of adenosine added to the cardioplegic solution, with the sixth arm being the pretreatment with adenosine. And we found what appeared to be clearly safety, but a suggestion of efficacy at that higher dose concentration, that is, the 2-mmol level.

And, finally, Dr. Merrill, with respect to the issue of would patients with a more compromised myocardium show a better benefit with response to myocardial protection, the answer is, we would speculate, yes. The initial study design involved enrollment of patients with an ejection fraction of less than 0.35. Enrollment was a problem, and certainly some of the criteria that were required for that enrollment would have limited a timely completion of the study.

Although the question was never asked directly—it was never our primary end point—we did observe less of a transfusion requirement, less platelet transfusions, in the postoperative period. But since there were no trigger points and this was not examined prospectively, we're reluctant to make any final comments.